EDITORIAL

Radiofrequency ablation or percutaneous ethanol injection for the treatment of liver tumors

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Abstract

The liver is a common location of both primary and secondary malignancies. For unresectable liver cancer, many local ablative therapies have been developed. These include e.g., percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), cryoablation, microwave ablation, laser-induced thermotherapy, and high-intensity focused ultrasound. RFA has recently gained interest and is the most widely applied thermoablative technique. RFA allows more effective tumor control in fewer treatment sessions compared with PEI, but with a higher rate of complications. However, there are certain circumstances where PEI therapy represents a better strategy to control liver tumors than RFA, especially in situations where RFA is difficult, for example when large vessels surround the tumor. In the context of hepatocellular carcinoma (HCC), both RFA and PEI are feasible and of benefit in non-operable patients. RFA seems superior to PEI in HCC > 2 cm, and the combination of interventions may be of benefit in selected patients. Liver resection is superior to RFA for patients with HCC meeting the Milan criteria, but RFA can be employed in tumors ≤ 3 cm and where there is an increased expected operative mortality. In addition, some lines of evidence indicate that RFA and PEI can be employed as a bridge to liver transplantation. The use of RFA in colorectal liver metastases is currently limited to unresectable disease and for patients unfit for surgery. The aim of this article is to summarize the current status of RFA in the management of liver tumors and compare it to the cheap and readily available technique of PEI.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third highest cause of cancer-related death and the incidence appears to be rising[1,2]. Partial hepatectomy and liver transplantation are potential curative options, but only a minority (10%-20%) are candidates for these therapies[3]. For inoperable cases, sorafenib (Nexavar®) is now available, inhibiting tumor-cell proliferation and tumor angiogenesis, as well as increasing the rate of apoptosis. It acts by inhibiting the serine-threonine kinase Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptor β[4,5]. Sorafenib increased median survival

and the time to radiological progression by nearly three months (7.9-10.7 mo and 2.8-5.5 mo, respectively) in patients with inoperable HCC[5]. The effect of sorafenib has been reproduced[6]. Furthermore, sorafenib has been reported to be cost-effective as compared to best supportive care in HCC[7]. Its multikinase inhibition, which is effective in RAS-mediated signal transduction pathways, is potentially applicable in other tumors[8,9]. Currently, the combination of sorafenib and various other chemotherapeutic agents in HCC is under investigation[10]. In the future, sorafenib might become an adjuvant following resection or local ablation of HCC[11].

Liver metastases occur in almost half of cases with colorectal cancer[12]. Resection is the treatment of choice for the 20% to 30% that have metastatic disease limited to the liver[13]. Novel local treatment, embolization, and not least, neoadjuvant radiochemotherapy have increased the number of resectable cases[14,15]. For those with initially unresectable colorectal liver metastases (CLM), downstaging with chemotherapy followed by rescue liver resection is safe and effective[16]. The role of chemotherapy in resectable CLM is not entirely certain. The use of perioperative FOLFOX has been associated with improvement of 3-year progression-free survival[17].

Over the years, local ablative methods have been developed for patients that are not surgical candidates because of multifocal disease, an inadequate liver remnant (size, function), or co-morbid conditions. These techniques include percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), cryoablation, microwave ablation, laser-induced thermotherapy, high-intensity focused ultrasound, and irreversible electroporation[18]. RFA has recently received increased attention, and is the most studied of the thermal ablation techniques[19]. This article reviews the current role of RFA in the treatment of liver tumors and compares it to PEI, which is a safe, cost-efficient, and readily available alternative to RFA.

RADIOFREQUENCY ABLATION AND PERCUTANEOUS ETHANOL INJECTION

Modern RFA for the treatment of liver tumors has been available since the early 1990's[20,21]. RFA induces thermal injury to the target tissue using electromagnetic energy with a frequency < 900 kHz. An electrode is placed into the lesion and a high-frequency alternating current is delivered. The current causes ionic agitation and frictional heat, leading to irreversible cellular changes, such as protein denaturation and coagulative necrosis of tumor cells. Optimal ablation results are achieved when local temperatures of 60 ℃ to 100 ℃ are employed. At temperatures above 100 ℃, the increase in the electrical impedance because of tissue carbonization and vaporization limits the amount of energy that can be delivered. Internally cooled-wet electrodes have been developed that combine interstitial saline infusion and intra-electrode cooling, thereby avoiding tissue desiccation around the electrode

tip and maintaining low impedance during treatment, while increasing the ablative zone[22,23]. RFA can be performed either percutaneously or intraoperatively with laparoscopy or laparotomy. The percutaneous approach is less invasive and may be associated with reduced postoperative pain, fewer complications, shorter hospital stay, and reduced costs[24-26]. However, surgical RFA allows more accurate cancer staging because of the direct macroscopic visualization of tumors and the use of intraoperative ultrasound. In patients with small HCC (≤ 3 cm), percutaneous and surgical RFA had similar complete ablation rates and the overall and disease-free survival were comparable at 1 and 3 years[25]. However, for larger tumors (3.1-5 cm), the surgical approach was associated with better overall survival. In addition, surgical RFA may be preferred for HCC occurring in high-risk locations, defined as less than 5 mm from a large vessel or an extrahepatic organ[27].

PEI was described for the first time in 1983[28]. PEI is performed under local anesthesia using a 21-gauge needle guided by ultrasound or computed tomography. Ethanol diffuses into the tumor cells and causes dehydration and protein denaturation, resulting in coagulative necrosis. This is followed by microvascular thrombosis and subsequent tumor ischemia. The amount of ethanol required can be calculated using the formula of a sphere, where 0.5 is added to provide extra safety margin: $V = 4/3 \times \pi \times (r + 0.5)^3$. The advantages of PEI are its relative safety, simplicity, and low cost. However, PEI is limited to small lesions and requires multiple sessions because of its reduced diffusion capacity over intratumoral septa.

Tumor seeding has occasionally been reported following RFA and PEI, but the risk remains low (< 2%) when an adequate ablation technique is employed and there is no previous biopsy[29-33]. Several studies have confirmed the safety of RFA and PEI in patients awaiting liver transplantation[34-41]. According to the practice guidelines from the American Association for the Study of Liver Diseases (AASLD), there is level Ⅱ evidence to support the use of RFA and PEI as a bridge to liver transplantation[42]. However, the actual value of local therapies before liver transplantation remains controversial. It has been suggested that bridging therapies such as RFA or PEI should be reserved for patients with a predicted waiting list time of more than 6 mo[43,44].

RADIOFREQUENCY ABLATION *VS* LIVER RESECTION

Two recent systematic reviews[45,46] showed no significant differences in survival between RFA and resection for HCC within the Milan criteria, although RFA was associated with higher recurrence rates. When RFA was used for tumors outside the Milan criteria, overall and disease-free survival rates were significantly better after resection[46]. Zhou *et al*[47] performed a meta-analysis of one randomized controlled trial (RCT) and nine controlled studies comparing RFA and liver resection for HCC

Table 1 Summary of meta-analyses of radiofrequency ablation *vs* liver resection and radiofrequency ablation *vs* percutaneous ethanol injection

Author	Diagnosis	Treatment	*n*	Tumor response (OR)	Complications (OR)	Local recurrence (OR)	Overall survival (OR)
Zhou *et al*[47]	HCC	RFA	744	-	0.29 (0.13-0.65)	4.50 (2.45-8.27)	0.60 (0.36- 1.01) (5 yr)
		resection	667				
Wu *et al*[50]	CLM	RFA	273	-	0.32 (0.07-1.52)	4.89 (1.73-13.87)	0.41 (0.22-0.90) (5 yr)
		resection	574				
Bouza *et al*[63]	HCC	RFA	396	1.10 (1.04-1.17)	Total: 2.55 (1.8-3.65)	0.37 (0.23-0.59)	1.24 (1.05-1.48) (4 yr)
		PEI	391		Major: 1.85 (0.68-5.01)		

PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; OR: Odds ratio; HCC: Hepatocellular carcinoma; CLM: Colorectal liver metastases.

(Table 1). Seven hundred and forty-four patients treated with RFA and 667 treated with resection were included. The 5-year overall survival rate was borderline significant at 5 years [OR 0.60 (0.36-1.01)]. RFA was associated with higher local recurrence [OR 4.50 (2.45-8.27)] and the disease-free survival rates were significantly better for resected patients. A recently published RCT by Huang *et al*[48] based on 230 patients fulfilling the Milan criteria, confirmed the superiority of surgical resection. The benefits of liver resection are further supported by data concerning quality of life adjusted survival, which seem to favor resection over RFA, at least in cirrhotic patients[49]. However, although current evidence favors liver resection for the treatment of early HCC (within the Milan criteria), percutaneous RFA can be used as a first-line treatment when the tumor is ≤ 3 cm and the expected operative mortality rate is above 3%[45].

Data concerning RFA *vs* resection for CLM are accumulating. A recent meta-analysis by Wu *et al*[50] compared RFA and liver resection for solitary CLM (Table 1). Liver resection was better than RFA in terms of 5-year overall survival, as well as local control of the disease. There were no statistically verified differences regarding the rate of adverse events. According to the study by Gazelle *et al*[51], liver resection is more effective in terms of quality-adjusted life year (QALY) as compared to RFA.

PERCUTANEOUS ETHANOL INJECTION *VS* LIVER RESECTION

PEI is suggested to be as safe and effective as resection in early-stage HCC (*n* = 76)[27]. On the other hand, Cho *et al*[52] reported that liver resection had a better survival profile as compared to PEI in 230 HCC patients (5-year overall survival 49% *vs* 19%). Repeated single-session PEI is effective in patients with advanced HCC and a combination of transcatheter arterial chemoembolization (TACE) and PEI results in longer survival[53].

The effectiveness of PEI for the treatment of CLM is unclear. It was reported that in more than 50% of cases of liver metastases < 4 cm, complete necrosis can be obtained by means of PEI[54]. Giorgio *et al*[55] reported that the survival rates of patients with liver metastases who underwent PEI were 94%, 80%, 80%, and 44% at 12 mo, 24 mo, 36 mo, and 44 mo, respectively. However, Livraghi *et al*[56] reported that PEI was ineffective for

the treatment of colorectal metastases. The main difficulty is that liver metastases are typically scirrhous and the alcohol tends to spread into the "soft" adjacent liver parenchyma. HCC is often surrounded by a cirrhotic parenchyma and is more vascularized than CLM, allowing for a better local effect of PEI[57,58].

RADIOFREQUENCY ABLATION *VS* PERCUTANEOUS ETHANOL INJECTION IN HEPATOCELLULAR CARCINOMA

Giorgio *et al*[59] recently conducted an RCT of percutaneous RFA and PEI in 285 HCC patients with tumors ≤ 3 cm. The primary endpoint was 5-year survival. In the RFA and PEI groups, the 5-year survival rates were 70% and 68%, respectively (not significant). The local recurrence rates were also not significantly different. The overall costs of RFA and PEI were 171 000 Euros and 1359 Euros, respectively ($P < 0.0001$). According to pooled data from two previous RCTs[60,61], RFA and PEI are equally effective for tumors ≤ 2 cm[62]. However, the effect of RFA is more predictable than PEI when considering all tumor sizes. The meta-analysis by Bouza *et al*[63] included a total of 396 patients treated by RFA and 391 treated by PEI (Table 1). RFA yielded a better overall survival (1 year, 2 year, 3 year, and 4 year), as well as disease-free survival (1 year, 2 year, and 3 year). The risk of local recurrence was reduced in the RFA group. Total complications were increased for RFA, but major complications were not significantly different. In terms of cost-effectiveness of PEI over RFA, data are still controversial. Brunello *et al*[64] reported that mean direct hospital costs were 6540 Euros for RFA treated patients and 4097 Euros for the PEI group ($P < 0.001$), whereas Seror *et al*[65] reported that RFA was the most cost-effective option.

RADIOFREQUENCY ABLATION-IMPROVEMENT WHEN COMBINED WITH PERCUTANEOUS ETHANOL INJECTION

RFA enables more effective tumor necrosis in fewer treatment sessions, albeit with a higher rate of complications than with PEI therapy. Nevertheless, there are certain circumstances or clinical situations that PEI therapy

offers a better strategy to control liver tumors than RFA, especially in situations where RFA is difficult. PEI can be useful when tumors are in close vicinity (< 1 cm) to vital structures, including biliary ducts, stomach, intestinal loops, and kidney, and whose location make them difficult to treat with thermal ablative techniques[66]. In addition, PEI is useful for lesions that remain undetected by ultrasound, such as masses in the hepatic dome or small nodules, or when the tumor is located subcapsularly or exophytically or surrounded by major vessels[66]. The efficacy of RFA in HCC can be improved if combined with PEI. The combination of RFA and PEI was shown to be more effective than RFA alone for high risk locations[67]. The combination of RFA and PEI can also be used for recurrent HCC (diameter > 3 cm)[68]. Furthermore, RFA and PEI can be combined with other locoregional therapies. TACE and RFA were as effective as liver resection for HCC in a recent study, with similar 1-, 3-, and 5-year overall and recurrence-free survival rates[69]. The combination of microwave ablation and PEI was safe and effective for the treatment of liver tumors adjacent to the hepatic hilum[70].

CONCLUSION

Liver resection still remains the gold standard for the treatment of liver tumors. RFA and PEI are feasible and of benefit in non-operable patients, and as bridging therapies before liver transplantation. RFA seems superior to PEI in HCC > 2 cm and the combination of both interventions may be of benefit in selected patients. Liver resection is superior to RFA for patients with HCC meeting the Milan criteria, but RFA can be employed in tumors ≤ 3 cm and where there is increased expected operative mortality. Using RFA as the primary treatment of resectable CLM is still not recommended; however, RFA may have a role in unresectable lesions and for patients unfit for surgery. Newer advancements in the field of local ablative therapies are to be expected, requiring constant evaluation of the different techniques. In the future, local ablative approaches may be combined with systematically administered molecular targeted therapies (e.g., sorafenib) to further improve the outcomes of patients with liver malignancies.

REFERENCES

1   **Bosch FX**, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology* 2004; **127**: S5-S16
2   **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108
3   **Toso C**, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. *J Hepatol* 2010; **52**: 930-936
4   **Abou-Alfa GK**, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293-4300
5   **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390
6   **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34
7   **Muszbek N**, Shah S, Carroll S, McDonald H, Dale P, Maroun J, Knox J. Economic evaluation of sorafenib in the treatment of hepatocellular carcinoma in Canada. *Curr Med Res Opin* 2008; **24**: 3559-3569
8   **Rini BI**. Sorafenib. *Expert Opin Pharmacother* 2006; **7**: 453-461
9   **Roberts LR**. Sorafenib in liver cancer--just the beginning. *N Engl J Med* 2008; **359**: 420-422
10   **Richly H**, Schultheis B, Adamietz IA, Kupsch P, Grubert M, Hilger RA, Ludwig M, Brendel E, Christensen O, Strumberg D. Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma: results from a phase I extension trial. *Eur J Cancer* 2009; **45**: 579-587
11   **Llovet JM**, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; **48** Suppl 1: S20-S37
12   **Swan PJ**, Welsh FK, Chandrakumaran K, Rees M. Long-term survival following delayed presentation and resection of colorectal liver metastases. *Br J Surg* 2011; **98**: 1309-1317
13   **Rees M**, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008; **247**: 125-135
14   **Adam R**, Lucidi V, Bismuth H. Hepatic colorectal metastases: methods of improving resectability. *Surg Clin North Am* 2004; **84**: 659-671
15   **Chua TC**, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 492-501
16   **Lam VW**, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A Systematic Review of Clinical Response and Survival Outcomes of Downsizing Systemic Chemotherapy and Rescue Liver Surgery in Patients with Initially Unresectable Colorectal Liver Metastases. *Ann Surg Oncol* 2011; Epub ahead of print
17   **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016
18   **Padma S**, Martinie JB, Iannitti DA. Liver tumor ablation: percutaneous and open approaches. *J Surg Oncol* 2009; **100**: 619-634
19   **Webb H**, Lubner MG, Hinshaw JL. Thermal ablation. *Semin Roentgenol* 2011; **46**: 133-141
20   **McGahan JP**, Browning PD, Brock JM, Tesluk H. Hepatic ablation using radiofrequency electrocautery. *Invest Radiol* 1990; **25**: 267-270
21   **Rossi S**, Fornari F, Pathies C, Buscarini L. Thermal lesions induced by 480 KHz localized current field in guinea pig and pig liver. *Tumori* 1990; **76**: 54-57
22   **Ni Y**, Miao Y, Mulier S, Yu J, Baert AL, Marchal G. A novel "cooled-wet" electrode for radiofrequency ablation. *Eur Radiol* 2000; **10**: 852-854

23   **Yoon HM**, Kim JH, Shin YM, Won HJ, Kim PN. Percutaneous radiofrequency ablation using internally cooled wet electrodes for treatment of colorectal liver metastases. *Clin Radiol* 2012; **67**: 122-127

24   **Crucitti A**, Danza FM, Antinori A, Vincenzo A, Pirulli PG, Bock E, Magistrelli P. Radiofrequency thermal ablation (RFA) of liver tumors: percutaneous and open surgical approaches. *J Exp Clin Cancer Res* 2003; **22**: 191-195

25   **Khan MR**, Poon RT, Ng KK, Chan AC, Yuen J, Tung H, Tsang J, Fan ST. Comparison of percutaneous and surgical approaches for radiofrequency ablation of small and medium hepatocellular carcinoma. *Arch Surg* 2007; **142**: 1136-1143; discussion 1143

26   **Wong J**, Lee KF, Lee PS, Ho SS, Yu SC, Ng WW, Cheung YS, Tsang YY, Ling E, Lai PB. Radiofrequency ablation for 110 malignant liver tumours: preliminary results on percutaneous and surgical approaches. *Asian J Surg* 2009; **32**: 13-20

27   **Huang GT**, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, Chen PJ, Kao JH, Sheu JC, Lee CZ, Chen DS. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. *Ann Surg* 2005; **242**: 36-42

28   **Ebara M,** Okabe S, Kita K, Sugiura N, Fukuda H, Yoshikawa M, Kondo F, Saisho H. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005; **43**: 458-464

29   **Latteri F**, Sandonato L, Di Marco V, Parisi P, Cabibbo G, Lombardo G, Galia M, Midiri M, Latteri MA, Craxì A. Seeding after radiofrequency ablation of hepatocellular carcinoma in patients with cirrhosis: a prospective study. *Dig Liver Dis* 2008; **40**: 684-689

30   **Livraghi T**, Lazzaroni S, Meloni F, Solbiati L. Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Br J Surg* 2005; **92**: 856-858

31   **Poon RT**, Ng KK, Lam CM, Ai V, Yuen J, Fan ST. Radiofrequency ablation for subcapsular hepatocellular carcinoma. *Ann Surg Oncol* 2004; **11**: 281-289

32   **Stigliano R**, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. *Cancer Treat Rev* 2007; **33**: 437-447

33   **Kim YJ**, Raman SS, Yu NC, Busuttil RW, Tong M, Lu DS. Radiofrequency ablation of hepatocellular carcinoma: can subcapsular tumors be safely ablated? *AJR Am J Roentgenol* 2008; **190**: 1029-1034

34   **Brillet PY**, Paradis V, Brancatelli G, Rangheard AS, Consigny Y, Plessier A, Durand F, Belghiti J, Sommacale D, Vilgrain V. Percutaneous radiofrequency ablation for hepatocellular carcinoma before liver transplantation: a prospective study with histopathologic comparison. *AJR Am J Roentgenol* 2006; **186**: S296-S305

35   **Fisher RA**, Maluf D, Cotterell AH, Stravitz T, Wolfe L, Luketic V, Sterling R, Shiffman M, Posner M. Non-resective ablation therapy for hepatocellular carcinoma: effectiveness measured by intention-to-treat and dropout from liver transplant waiting list. *Clin Transplant* 2004; **18**: 502-512

36   **Fontana RJ**, Hamidullah H, Nghiem H, Greenson JK, Hussain H, Marrero J, Rudich S, McClure LA, Arenas J. Percutaneous radiofrequency thermal ablation of hepatocellular carcinoma: a safe and effective bridge to liver transplantation. *Liver Transpl* 2002; **8**: 1165-1174

37   **Lu DS**, Yu NC, Raman SS, Lassman C, Tong MJ, Britten C, Durazo F, Saab S, Han S, Finn R, Hiatt JR, Busuttil RW. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *Hepatology* 2005; **41**: 1130-1137

38   **Mazzaferro V**, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M, Garbagnati F, Marchianò A, Spreafico C, Camerini T, Mariani L, Miceli R, Andreola S.

Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004; **240**: 900-909

39   **Pompili M**, Mirante VG, Rondinara G, Fassati LR, Piscaglia F, Agnes S, Covino M, Ravaioli M, Fagiuoli S, Gasbarrini G, Rapaccini GL. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl* 2005; **11**: 1117-1126

40   **Branco F**, Brú C, Vilana R, Bianchi L, Alves de Mattos A. Percutaneous ethanol injection before liver transplantation in the hepatocellular carcinoma. *Ann Hepatol* 2009; **8**: 220-227

41   **Castroagudin JF**, Delgado M, Martinez SM, Abdulkader I, Potel J, Tome S, Otero E, Varo E. Prospective histopathological analysis of hepatocellular carcinoma treated with percutaneous ethanol injection in patients on the waiting list for liver transplantation. *Transplant Proc* 2005; **37**: 1477-1479

42   **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022

43   **Belghiti J**, Carr BI, Greig PD, Lencioni R, Poon RT. Treatment before liver transplantation for HCC. *Ann Surg Oncol* 2008; **15**: 993-1000

44   **Lau WY**, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. *Ann Surg* 2009; **249**: 20-25

45   **Cho YK**, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. *J Gastroenterol Hepatol* 2011; **26**: 1354-1360

46   **Tiong L**, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. *Br J Surg* 2011; **98**: 1210-1224

47   **Zhou Y**, Zhao Y, Li B, Xu D, Yin Z, Xie F, Yang J. Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. *BMC Gastroenterol* 2010; **10**: 78

48   **Huang J**, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; **252**: 903-912

49   **Molinari M**, Helton S. Hepatic resection versus radiofrequency ablation for hepatocellular carcinoma in cirrhotic individuals not candidates for liver transplantation: a Markov model decision analysis. *Am J Surg* 2009; **198**: 396-406

50   **Wu YZ**, Li B, Wang T, Wang SJ, Zhou YM. Radiofrequency ablation vs hepatic resection for solitary colorectal liver metastasis: a meta-analysis. *World J Gastroenterol* 2011; **17**: 4143-4148

51   **Gazelle GS**, McMahon PM, Beinfeld MT, Halpern EF, Weinstein MC. Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection. *Radiology* 2004; **233**: 729-739

52   **Cho YB**, Lee KU, Suh KS, Kim YJ, Yoon JH, Lee HS, Hahn S, Park BJ. Hepatic resection compared to percutaneous ethanol injection for small hepatocellular carcinoma using propensity score matching. *J Gastroenterol Hepatol* 2007; **22**: 1643-1649

53   **Dettmer A**, Kirchhoff TD, Gebel M, Zender L, Malek NP, Panning B, Chavan A, Rosenthal H, Kubicka S, Krusche S, Merkesdal S, Galanski M, Manns MP, Bleck JS. Combination of repeated single-session percutaneous ethanol injection and transarterial chemoembolisation compared to repeated single-session percutaneous ethanol injection in patients with non-resectable hepatocellular carcinoma. *World J Gastroenterol* 2006; **12**: 3707-3715

54   **Giovannini M**. Percutaneous alcohol ablation for liver metastasis. *Semin Oncol* 2002; **29**: 192-195

55   **Giorgio A**, Tarantino L, Mariniello N, De Stefano G, Perrotta A, Aloisio V, Del Viscovo L, Alaia A. [Ultrasonography-

guided percutaneous ethanol injection in large an/or multiple liver metastasis]. *Radiol Med* 1998; **96**: 238-242

56   **Livraghi T**, Vettori C, Lazzaroni S. Liver metastases: results of percutaneous ethanol injection in 14 patients. *Radiology* 1991; **179**: 709-712

57   **Lau WY**, Leung TW, Yu SC, Ho SK. Percutaneous local ablative therapy for hepatocellular carcinoma: a review and look into the future. *Ann Surg* 2003; **237**: 171-179

58   **Garcea G**, Lloyd TD, Aylott C, Maddern G, Berry DP. The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours. *Eur J Cancer* 2003; **39**: 2150-2164

59   **Giorgio A**, Di Sarno A, De Stefano G, Scognamiglio U, Farella N, Mariniello A, Esposito V, Coppola C, Giorgio V. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial. *Anticancer Res* 2011; **31**: 2291-2295

60   **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or = 4 cm. *Gastroenterology* 2004; **127**: 1714-1723

61   **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; **54**: 1151-1156

62   **Germani G**, Pleguezuelo M, Gurusamy K, Meyer T, Isgrò G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a meta-analysis. *J Hepatol* 2010; **52**: 380-388

63   **Bouza C**, López-Cuadrado T, Alcázar R, Saz-Parkinson Z, Amate JM. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol* 2009; **9**: 31

64   **Brunello F**, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, Sacchetto P, Gandini G, Rizzetto M. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scand J Gastroenterol* 2008; **43**: 727-735

65   **Seror O**, N'Kontchou G, Tin Tin Htar M, Durand-Zaleski I, Trinchet JC, Sellier N, Beaugrand M. Ethanol versus radiofrequency ablation for the treatment of small hepatocellular carcinoma in patients with cirrhosis: a retrospective study of efficacy and cost. *Gastroenterol Clin Biol* 2006; **30**: 1265-1273

66   **Kwon JH**. Is percutaneous ethanol injection therapy still effective for hepatocellular carcinoma in the era of radiofrequency ablation? *Gut Liver* 2010; **4** Suppl 1: S105-S112

67   **Wong SN**, Lin CJ, Lin CC, Chen WT, Cua IH, Lin SM. Combined percutaneous radiofrequency ablation and ethanol injection for hepatocellular carcinoma in high-risk locations. *AJR Am J Roentgenol* 2008; **190**: W187-W195

68   **Luo BM**, Wen YL, Yang HY, Zhi H, Xiao XY, Ou B, Pan JS, Ma JH. Percutaneous ethanol injection, radiofrequency and their combination in treatment of hepatocellular carcinoma. *World J Gastroenterol* 2005; **11**: 6277-6280

69   **Yamakado K**, Nakatsuka A, Takaki H, Yokoi H, Usui M, Sakurai H, Isaji S, Shiraki K, Fuke H, Uemoto S, Takeda K. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. *Radiology* 2008; **247**: 260-266

70   **Ren H**, Liang P, Yu X, Wang Y, Lu T, Li X. Treatment of liver tumours adjacent to hepatic hilum with percutaneous microwave ablation combined with ethanol injection: a pilot study. *Int J Hyperthermia* 2011; **27**: 249-254